

A multimedia, multiple pathway risk assessment of atrazine: the impact of age differentiated exposure including joint uncertainty and variability

Deborah H. Bennett^a, W.E. Kastenberg^{b,*}, T.E. McKone^c

^a*Department of Mechanical Engineering, University of California, Berkeley, CA 94720, USA*

^b*Department of Nuclear Engineering and The Center for Nuclear and Toxic Waste Management, University of California, Berkeley, CA 94720, USA*

^c*School of Public Health and The Lawrence Berkeley National Laboratory, University of California, Berkeley, CA 94720, USA*

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Abstract

This paper addresses the need to evaluate the differences in exposure to pesticides between children and adults. We present a framework for evaluating these differences in exposure to pesticides through multiple exposure pathways. The concentrations in all environmental media were determined as distributions in a companion paper. All parameter values utilized in the calculation of exposure and risk are considered to be distributions, resulting in distributions for output exposure and risk. A sensitivity analysis was completed to determine the relative importance of the parameters with respect to the outcome. A joint uncertainty and variability analysis was also completed to evaluate the relative contribution between uncertain and variable parameters. Exposure to atrazine by a mid-western farming family is presented as a case study. The predicted exposure for a child based on a 14-year exposure period was 1.6 times that calculated using lifetime averaged exposure parameters. This indicates the importance of considering children as a population sub-group when calculating the exposure and risk to pesticides. © 1998 Elsevier Science Ltd.

Keywords: Risk assessment; Atrazine; Age differentiated exposure; Multi-pathway exposure

1. Introduction

Reports of agrochemical residues detected in food and water have heightened the public's awareness of the possible risks to human and ecological receptors from agrochemicals. There have been numerous reports that focus on the ability of agrochemicals to provide near year-round, high quality produce and claiming minimal risk, thus supporting the use of these pesticides [1,2]. Nevertheless, other reports focus on the possible dangers of pesticides and the lack of health-based standards for ground water, surface water and food residues for a majority of these products [3]. More than 1 billion pounds of pesticides are used yearly in the United States, over half being herbicide applications [4].

The National Research Council published 'Pesticides in the Diets of Infants and Children' [5], pointing out the need to further examine the possible discrepancy in risk between adults and children. To properly account for the risk to children, there is a need for a set of exposure parameters

that account for both physiological and behavioral differences between children and adults. At present, however, there is a lack of a consistent multimedia, multiple exposure pathway methodology for determining the differences in risk for different age and gender groups.

Determining exposure in a multimedia environment requires inclusion of variability in individual exposure. Such variability occurs due to population movement, individual lifestyles (housing, food and water supply, and consumption rate), and the temporal and spatial character of the source. The time dependence and individual variations of exposure pathways can be represented by random variables for body weight, average body surface area, and so forth.

In a companion paper [6], we examined the fate and transport of atrazine in the mid-western region of the United States. The results indicated that atrazine, a widely used pesticide, spreads to ground water, surface water, soil, and plants, making it an ideal candidate for a case study to examine the effect of multiple pathway exposure and hence, risk. In this paper, the incremental lifetime cancer risk to a typical mid-western family resulting from exposure to atrazine is evaluated. In the companion paper, the steady-state concentration of atrazine in different environmental

* Corresponding author. 4153 Etcheverry Hall, University of California, Berkeley, CA 94720-1730, USA. Tel.: +1-510-643-0574; Fax: +1-510-643-9685; E-mail: kastenbe@nuc.berkeley.edu

media was determined. The outcome variance, and the sources of this variance, were quantified. Concentrations in ground and surface water were compared to measured field concentrations and were found to be of the same order of magnitude. Having determined the concentration distribution for each environmental medium in the previous paper, our objectives in this second paper are as follows:

1. Utilize a multimedia, multiple exposure pathway model (CalTOX) to investigate both the exposure pathways which contribute significantly to risk, and the total integrated risk. The integration of several exposure pathways results in a more comprehensive risk assessment.
2. Provide exposure parameters which are statistically averaged over childhood, and over a lifetime (combining both childhood and adult exposures), based on information found in a literature survey. This differentiation allows us to compare the risk based on age differences.
3. Address uncertainty and variability separately in determining exposure and risk, and evaluate how uncertainties interact with one another in a joint uncertainty and variability analysis. Additionally we complete a sensitivity analysis to determine the parameters whose uncertainty, when reduced, will reduce the outcome variance.
4. Determine the risk to both adults and children and evaluate any significant differences that need to be considered in risk management strategies.

2. Background

To complete a health risk assessment, several steps need to be integrated. First, the source term must be characterized. Second, environmental concentrations are established using (a) monitoring data, (b) a fate and transport model, or (c) some combination of monitoring data and models. Third, the relationship between environmental concentrations and human exposure media concentrations, such as tap water, indoor air, and food must be determined. Fourth, rates of human uptake from these contaminated media are established for each exposure pathway and population subgroup. Finally, the dose is multiplied by a dose-response factor (i.e. cancer potency factor) to determine the risk.

Several of the parameters used to determine the dose and corresponding risk are uncertain and/or variable, and thus should not be represented as point values. Uncertainty in parameters can result from measurement uncertainty, insufficient data, or incomplete knowledge of the processes and mechanisms that give rise to these parameters. Variability in parameters can result from human behavioral and physiological differences and can vary from individual to individual at the same location. Adverse effects of agricultural chemicals on human health due to exposure are often unclear since they have been designed to produce certain biological actions on non-human targets (e.g. weeds, insects, fungi, etc.) Furthermore, the response to the same dose can be different between individuals.

Both uncertainty and variability are included and treated independently in this analysis. It is important to distinguish between inter-individual variability and parameter uncertainty in a risk assessment to determine the risk to an individual. Uncertainty refers to errors of omission, specification, measurement or extrapolation, while variability refers to spatial, temporal, physiological, and behavioral distributions of factors within a landscape or population [7]. Examples of uncertain variables are the octanol water partitioning coefficients and other physical chemical properties, while variable parameters include breathing rates. In this paper, uncertainty and variability are propagated through the risk calculations using a nested Monte Carlo method.

3. Approach

The source term and environmental media concentrations for atrazine are based on application data and the use of a fate and transport model. These two steps were considered in the companion paper [6]. In this paper, the concentrations in the exposure media of a typical residential mid-western family are determined. The potential dose is based on the rate of uptake from these contaminated environmental media. For a carcinogenic risk assessment, the exposure duration is typically averaged over a 70 year lifetime period [8]. The potential dose from all exposure pathways is then multiplied by the cancer potency factor, yielding the incremental lifetime cancer risk. In this paper, distributions are used for parameter inputs and thus the risk estimated from propagating these values through a Monte Carlo simulation are represented as distributions. Exposure parameters will be based on four sets of input data, children of each gender and lifetime averages for each gender. Because we are addressing exposure uncertainty/variability, the cancer potency factors used here have a single-value representation.

3.1. Source term and environmental media concentrations

The source term and environmental media concentrations were quantified in the companion paper. The source term was based on historical pesticide application rates and the acreage of treated fields. Because the source term is highly variable, the sensitivity analysis revealed this to be one of the most significant contributors to variance in the calculated environmental concentrations.

Fate and transport of atrazine is modeled with the CalTOX model, based on a set of fugacity equations linking environmental compartments [9–12]. As noted above, the concentrations in ground and surface water predicted by the model are the same order of magnitude as measured concentrations in the mid-western United States, indicating that modeling can predict the concentrations in the environment to within an order of magnitude. The multimedia

Table 1
Data for bioconcentration factors for atrazine in various organisms

Type	Numerical values	Units/organisms	Reference
Bioconcentration factor, BCF	2–15	snails	[48]
	10–83	algae	[48]
	3–10	fish	[13]
	11	<i>Gmmarus affinus</i>	[13]
	7.5	snails	[13]
	11	fish	[13]
	76	algae	[13]
	4.2	daphnids @ 0.01 mg l ⁻¹ conc.	[13]
	2.2	daphnids @ 0.08 mg l ⁻¹ conc.	[13]
	3–4	mollusc	[13]
	2.8	whole fish	[13]
	2–20	<i>L. reticulata</i> for various exposure regimes	[13]
	0.8–96	Crayfish <i>Orconectes virilis</i> @ 49.54 ± 39.75 µg l ⁻¹ conc.	[13]
	5.2–480	Mayfly nymphs <i>Baetis</i> sp.	[13]
	2.0 (log BCF)	<i>Cottus bairdi</i>	[16]
	1.0 (log BCF)	<i>Leuciscus idus melanotus</i>	[16]
	0.9 (log BCF)	<i>Pimephales promelas</i>	[16]
	0.5 (log BCF)	<i>Coregonus fera</i>	[16]
	0.3 (log BCF)	<i>Ictalurus melas</i>	[16]
	1.9 (log BCF)	predicted from S_w	[16]
	0.8 (log BCF)	predicted from K_{oc}	[16]

Table 2
Mean and standard deviation of the bioconcentration factor for atrazine

Parameter	Distribution shape	Statistical variables
Bioconcentration factor	uniform	3 (minimum) 100 (maximum)

environment model provides a basis for multiple pathway exposure calculations.

3.2. Exposure media concentrations

Human exposure is calculated from the agrochemical concentration of each exposure medium. Exposure media include indoor air, tap water, produce, animal products, and household soils. For example, the concentration of the contaminant in tap water is related to the atrazine concentration in the surface and ground water. The contaminant concentration in household soil is related to soil tracked in by humans or pets and dust particles in the air that enters the house.

Determining the concentrations in various food products involves a variety of parameters, many of which are highly uncertain or variable. Produce is divided into exposed and unexposed produce; exposed produce includes above ground edible plant parts exposed to the air, while unexposed produce includes root crops and protected produce, such as citrus. Different parameters are needed to determine the concentrations in these two types of produce.

Atrazine dissolved in water is absorbed by aquatic organisms until steady state concentration ratios are reached. Fish bioaccumulate atrazine very rapidly. At steady-state, concentrations measured in the blood, gills, and muscle of fish

and other aquatic organisms are proportional to the external chemical concentration in the water [13]. The herbicide can bioaccumulate above external concentrations in fish liver, kidney, and intestine [14]. Atrazine is moderately lipophilic and accumulates in fish organs in proportion to the lipid content of the organ [14].

The bioconcentration factors (BCF) and biotransfer factors used in CalTOX provide a measure of chemical partitioning between a biological medium such as fish tissue, and an external medium such as water. The bioconcentration factor is used to predict the contaminant concentration in organisms relative to the concentration in the contaminated water. Bioconcentration factors for atrazine in various organisms found in the literature are presented in Table 1, along with relevant references, while the distribution used is in Table 2.

Determining the atrazine concentration in animal products requires an evaluation of the animal's contact rates through inhalation and ingestion, and accumulation rate in animal tissue. As noted above, atrazine is moderately lipophilic and thus concentrations increase in mammalian organs as the lipid content of the organ increases. Significant concentrations of atrazine remain in animal abdominal fat after cessation of exposure. Trotter et al. [13] detected high concentrations of atrazine metabolites in liver, kidney, and lung tissues. Absorption of atrazine residues in plant

material ingested by mammals has been demonstrated to be very small [13]. The biotransfer factor relates the steady-state contaminant concentration in fresh meat or milk to the animals' daily contaminant intake resulting from inhalation and ingestion pathways. Both the bioconcentration factor and the biotransfer factor are used to characterize the accumulative effects of atrazine on biological systems [15].

There is much uncertainty associated with the concentration in exposure media as related to environmental media. Sources of this uncertainty include: limited information on partitioning of contaminants between air and/or soil and vegetation (such as food and pasture crops), large variation in the biotransfer factors between animal intake and animal-based food products (such as meat, dairy products, and eggs), uncharacterized exposure pathways to animals and variable bioconcentration factors for different organisms and concentration levels. These factors all add to the complexity of the relationship between contaminated soil and human contact.

3.3. Human activity and contact

Human exposure to atrazine is based on the magnitude and direction of mass exchanged between the environment and humans by inhalation, ingestion, and dermal contact. While relatively large human exposure to atrazine occurs for a small number of people from occupational activities, such as herbicide production or application [16], these occupational exposure pathways are not being considered in this paper. We instead focus on the residential population that is exposed to agrochemicals through everyday activities bringing them in contact with contaminated environmental media as well as through food and drinking water. The level of contact with each exposure medium changes with age. Thus, exposure parameters averaged over a lifetime and averaged over childhood are both used. The exposure in a residential setting such as a family farm in Iowa is considered.

The following exposure equation links the time averaged dose to the exposure medium concentration and is used for each exposure pathway in this analysis. The basic form of the exposure equation is [17]:

$$I = C \times \frac{CR}{BW} \times \frac{ED \times EF}{AT} \quad (1)$$

where I is the intake of chemical via that exposure route ($\text{mg kg}^{-1} \text{ day}^{-1}$), C the chemical concentration in exposure medium (kg kg^{-1}), CR the contact rate (mg day^{-1}), BW the body weight (kg), ED the exposure duration (years), EF the exposure frequency (days per year), and AT the averaging time (days).

Eq. (1) is modified for each specific exposure scenario to include the necessary parameters for the pathway being considered. In this assessment, the CalTOX model is used to determine the amount of human uptake through each exposure pathway. By separating the input values into lifetime and childhood categories, one can evaluate the

exposure to children as a separate, possibly more sensitive subgroup.

The exposure routes considered in this paper are inhalation, ingestion, and dermal exposure pathways. Inhalation pathways include both indoor and outdoor air intake. Ingestion pathways include the consumption of vegetables, grains, tap water, soil, and animal products such as meat, poultry, eggs, and dairy. Ninety percent of the grain consumed by residents of the mid-west is produced locally [17]. Livestock is linked to the contaminated environment through multiple pathways, including inhalation and ingestion. Dermal pathways include exposures through water from showering, bathing and recreation, as well as from contaminated soil on the skin.

Exposure parameters for both children and adults of both gender groups were developed. This data provides a method of targeting exposure for a given population and for a given activity. It is important to note that these activities are not uniform across each age and gender group but are variable. This literature search provided data for both physiological exposure parameters (e.g. breathing rate, food and fluid intake rate) and activity parameters (e.g. time spent sleeping, time spent in recreation, time spent outdoors).

Four sets of exposure parameters were created. Two sets, male and female, are based on parameters pooled statistically over an individual's lifetime. The second two sets of parameters are pooled over the first 14 years of a child's life by gender. We used 14 years because this is the average exposure duration estimated in the United States [18]. The pooling equations used for combining age dependent values to create a uniform group are [19]:

$$x = au + bv \quad (2)$$

$$\sigma_x^2 = a\sigma_u^2 + b\sigma_v^2 \pm 2ab\sigma_{uv} \quad (3)$$

where a and b are the weighting factors for distributions u and v , respectively.

Body weight plays an important role in the calculation of chemical risk. The National Health and Nutrition Examination Survey (NHANES II) was conducted from February 1976 through February 1980 and collected information on the height and body weight of people across the country. Lognormal distributions have been used to represent all age groups based on this data [20,21].

Body weight is needed because cancer slope factors are based on the chemical concentration per unit body weight. There are two ways to calculate the chemical concentration per unit body weight in a risk calculation. One can calculate all of the intakes and then divide by the appropriate body weight. Alternatively, one can calculate all the intakes on a per body weight basis. The second type of calculation allows for correlation between the intake parameter and the body weight. This limits unrealistic cases that consider, for example, the lightest person having the highest food intake.

Skin surface area is highly correlated to body weight. The

Table 3
Intake parameter values for males

Parameter (units)	Male 0–14, mean	Coefficient of variation	Male lifetime mean	Coefficient of variation	References
Body weight (kg)	$2.64 \times 10^{+01}$	0.22	$6.72 \times 10^{+01}$	0.18	[20] [21]
Surface area ($\text{m}^2 \text{kg}^{-1}$)	4.54×10^{-02}	0.18	3.26×10^{-02}	0.14	[21]
Active breathing rate ($\text{m}^3 \text{kg}^{-1} \text{h}^{-1}$)	2.15×10^{-02}	0.46	1.05×10^{-02}	0.27	[30]
Resting breathing rate ($\text{m}^3 \text{kg}^{-1} \text{h}^{-1}$)	9.37×10^{-03}	0.52	5.75×10^{-03}	8.61	[30]
Fluid intake ($\text{l kg}^{-1} \text{day}^{-1}$)	3.37×10^{-02}	0.64	2.19×10^{-02}	0.60	[25]
Fruit and vegetable intake ($\text{kg kg}^{-1} \text{day}^{-1}$)	8.23×10^{-03}	0.54	4.20×10^{-03}	0.25	[23]
Grain intake ($\text{kg kg}^{-1} \text{day}^{-1}$)	7.60×10^{-03}	0.49	3.02×10^{-03}	0.30	[23]
Milk intake ($\text{kg kg}^{-1} \text{day}^{-1}$)	1.93×10^{-02}	0.48	5.22×10^{-03}	0.46	[23]
Meat intake ($\text{kg kg}^{-1} \text{day}^{-1}$)	4.89×10^{-03}	0.57	3.12×10^{-03}	0.22	[23]
Egg intake ($\text{kg kg}^{-1} \text{day}^{-1}$)	7.17×10^{-04}	0.12	4.90×10^{-04}	0.47	[23]
Fish intake ($\text{kg kg}^{-1} \text{day}^{-1}$)	3.87×10^{-04}	2.52	2.84×10^{-04}	0.89	[23]
Soil ingestion ($\text{kg kg}^{-1} \text{day}^{-1}$)	1.87×10^{-06}	2.75	5.03×10^{-07}	2.15	[26,27]
Soil adherence to skin (mg cm^{-2})	6.27×10^{-01}	1.86	5.17×10^{-01}	1.35	[29]

ratio between surface area to body weight has been found to fit different normal and lognormal distributions depending on age, but not gender [21].

Food and water consumption rates are based on the 1977–78 US Department of Agriculture [22] study entitled ‘Nationwide Food Consumption Survey’. Food intake rates for each age group were compiled and then correlated to body weight to the two-thirds power for this paper [23]. This correlation is only an approximation; however, it has been used by other researchers (for example, Ref. [24]). Data on tap water intake per unit body weight for different age groups has been compiled directly [25], eliminating any need for a correlation factor.

Several studies have been conducted to characterize soil ingestion by children, the most well known being that of Calabrese et al. [26]. Lognormal distributions were used to fit the data for a child’s intake and for a lifetime intake of soil [27,28]. A comprehensive review of studies on soil–skin adherence for different age groups was compiled by Finley et al. [29] and is used here.

Metabolically based breathing rates are based on food intake and the number of resting versus active hours, following the procedure of Layton [30]. The ratio of metabolism between resting and active hours is then used to determine two breathing rates [30].

The resulting distributions employed in this paper for the above parameters can be found in Tables 3, 4 and 5.

3.4. Dose response

The risks of atrazine to the exposed population include acute and chronic adverse health conditions, as well as an increased risk of cancer. Many epidemiological studies and animal experiments have been performed which attempt to establish the relationship between the amount of atrazine administered to a subject and the probability of the occurrence of either a tumor or cancer at that dose. Low-dose human cancer potency is extrapolated solely from high dose experimental data to project the risk associated with a unit of exposure [31]. It is important to note that all three

Table 4
Intake parameter values for females

Parameter (units)	Female 0–14, mean	Coefficient of variation	Female lifetime mean	Coefficient of variation	References
Body weight (kg)	$2.63 \times 10^{+01}$	0.23	$5.70 \times 10^{+01}$	0.24	[20] [21]
Surface area ($\text{m}^2 \text{kg}^{-1}$)	4.54×10^{-02}	0.18	3.26×10^{-02}	0.15	[21]
Active breathing rate ($\text{m}^3 \text{kg}^{-1} \text{h}^{-1}$)	2.04×10^{-02}	0.46	8.96×10^{-03}	0.33	[30]
Resting breathing rate ($\text{m}^3 \text{kg}^{-1} \text{h}^{-1}$)	8.88×10^{-03}	0.51	5.38×10^{-03}	0.30	[30]
Fluid intake ($\text{l kg}^{-1} \text{day}^{-1}$)	3.29×10^{-02}	0.69	2.31×10^{-02}	0.60	[25]
Fruit and vegetable intake ($\text{kg kg}^{-1} \text{day}^{-1}$)	8.23×10^{-03}	0.54	4.20×10^{-03}	0.25	[23]
Grain intake ($\text{kg kg}^{-1} \text{day}^{-1}$)	7.60×10^{-03}	0.49	3.02×10^{-03}	0.30	[23]
Milk intake ($\text{kg kg}^{-1} \text{day}^{-1}$)	1.78×10^{-02}	0.53	4.88×10^{-03}	0.54	[23]
Meat intake ($\text{kg kg}^{-1} \text{day}^{-1}$)	4.44×10^{-03}	0.64	2.55×10^{-03}	0.29	[23]
Egg intake ($\text{kg kg}^{-1} \text{day}^{-1}$)	6.36×10^{-04}	1.43	3.84×10^{-04}	0.66	[23]
Fish intake ($\text{kg kg}^{-1} \text{day}^{-1}$)	3.58×10^{-04}	2.73	2.95×10^{-04}	0.93	[23]
Soil ingestion ($\text{kg kg}^{-1} \text{day}^{-1}$)	1.87×10^{-06}	2.75	5.03×10^{-07}	2.15	[26,27]
Soil adherence to skin (mg cm^{-2})	6.27×10^{-01}	1.86	5.17×10^{-01}	1.35	[29]

Table 5
Other representative exposure parameters

Parameter (units)	Mean value	Coefficient of variation	References
Inhalation by cattle ($\text{m}^3 \text{day}^{-1}$)	122	0.3	[15]
Inhalation by hens ($\text{m}^3 \text{day}^{-1}$)	2.2	0.3	[15]
Ingestion of pasture, dairy cattle ($\text{kg}[\text{FM}] \text{day}^{-1}$)	85	0.2	[15]
Ingestion of pasture, beef cattle ($\text{kg}[\text{FM}] \text{day}^{-1}$)	60	0.4	[15]
Ingestion of pasture by hens ($\text{kg}[\text{FM}] \text{day}^{-1}$)	0.12	0.04	[37]
Ingestion of water by dairy cattle (l day^{-1})	35	0.2	[37]
Ingestion of water by beef cattle (l day^{-1})	35	0.2	[37]
Ingestion of water by hens (l day^{-1})	0.084	0.1	[37]
Ingestion of soil by cattle (kg day^{-1})	0.4	0.7	[15]
Ingestion of soil by hens (kg day^{-1})	0.000013	1	[44]
Fraction of water needs from ground water	0.8	0.1	[47]
Fraction of water needs from surface water	0.2	0.1	[47]
Fraction of irrigation water contaminants transferred to soil	0.25	1	[9]
Fraction fruits and vegetables that are exposed produce	0.47	0.1	[23]
Fraction of fruits and vegetables local	0.24	0.7	[17]
Fraction of grains local	0.8	0.7	[17]
Fraction of milk local	0.4	0.7	[17]
Fraction of meat local	0.44	0.5	[17]
Fraction of eggs local	0.4	0.7	[24]
Fraction of fish local	0.7	0.3	[17]
Plant – air particle partition factor, $\text{m}^3 \text{kg}^{-1}[\text{FM}]$	3300	1.8	[15]
Rainsplash ($\text{mg kg}^{-1}[\text{plant FM}]/\text{mg kg}^{-1}[\text{soil}]$)	0.0034	1	[38]
Water use in the shower (l min^{-1})	8	0.4	[40]
Water use in the House (l h^{-1})	40	0.4	[47]
Bathroom ventilation rate ($\text{m}^3 \text{min}^{-1}$)	1	0.4	[43]
Room ventilation rate, house ($\text{m}^3 \text{h}^{-1}$)	750	0.3	[43]
Exposure time, shower or bath (h day^{-1})	0.27	0.6	[40]
Exposure time, active indoors (h day^{-1})	8	0.14	[17]
Exposure time, outdoors at home (h day^{-1})	0.3	0.14	[17]
Exposure time, indoors resting (h day^{-1})	8	0.04	[17]
Indoor dust load (kg m^{-3})	3E^{-08}	0.4	[45]
Exposure frequency to soil on skin (days per year)	137	0.6	[46]
Ratio of indoor gas concentration to soil gas concentration	0.0001	2	[42]
Exposure time swimming (h day^{-1})	0.5	0.5	[46]
Exposure frequency, swimming (days per year)	15	4	[46]
Water ingestion while swimming ($\text{l kg}^{-1} \text{h}^{-1}$)	0.0007	1	[18]
Exposure duration (years)	14	1.15	[17]
Averaging time (days)	25550	0.1	

degradation products, deethyl-atrazine, deisopropyl-atrazine, and hydroxyatrazine, are at least of equal toxicity to atrazine itself, according to the manufacturer Ciba-Geigy [8].

The added cancer risk to an individual is determined through the relationship of the dose and the cancer potency factor. Based upon animal experiments, a cancer potency factor (CPF) is estimated for human health risk assessments. Carcinogenic potency refers to the quantitative expression of increased tumor generation per unit dose rate at very low dose levels.

The USEPA [32] has assigned atrazine a Group-C classification which designates the herbicide as a possible human carcinogen due to limited evidence of carcinogenicity in

animals and inadequate, or lack of, human data. In the 1993 annual update of the Health Effects Assessment Summary Tables (HEAST), the slope factor and unit risk value for carcinogenicity based on lifetime oral exposure are $6.3 \times 10^{-6} \text{ g}^{-1} \text{l}$ and $2.22 \times 10^{-1} \text{ mg}^{-1} \text{kg day}$, respectively [32]. The CPF values estimated from human or animal data are inherently uncertain [33]. A summary of relevant biological and toxicological data for atrazine is shown in Table 6, with the CPF distribution in Table 7.

3.5. Uncertainty and variability

Estimates of parameter values can rarely be characterized accurately by a single value. In this paper, a probability

Table 6
Data values for toxicological parameters

Type	Numerical values	Units/organisms	Reference
Cancer potency factor for lifetime oral exposure, CPF	6.3×10^{-6}	$(\mu\text{g/l})^{-1}$; the slope factor	[32]
	2.22×10^{-1}	$(\text{mg kg}^{-1} \text{ day}^{-1})^{-1}$; unit risk value	[32]
Acute oral LD ₅₀ (lethal dose)	1869	mg kg ⁻¹ ; rats	[39]
	3080	mg kg ⁻¹ ; rats	[48]
	1750	mg kg ⁻¹ ; mice	[48]
Acute dermal LD ₅₀	7500	mg kg ⁻¹ ; rabbits	[13]
96 h LC ₅₀ fish	8.8	mg l ⁻¹ ; rainbow trout	[41]
(lethal conc.)	16	blue gill sunfish	[41]
	76	carp	[41]
	7.6	catfish	[41]
	16	perch	[41]
	4.3	guppies	[41]
	0.22–100	mg l ⁻¹ ; for fish species	[13]
	4.5	Rainbow trout, <i>Salmo gairdneri</i>	[13]
	4.3	guppy, <i>Lebistes reticulata</i>	[13]
LC ₅₀ for 5–7 day exposures	700–19650	mg l ⁻¹ per body weight; birds	[13]
Lethal dose for ingestion	2 doses of 250	mg kg ⁻¹ within 24 h by cattle	[13]
Chronic oral intakes failed to	100	mg kg ⁻¹ (for 21 days)	[13]
induce significant adverse effects in cattle	760	mg kg ⁻¹ (for 4 weeks)	[13]

distribution is assigned to each uncertain or variable parameter with a shape and range based on measured values for that parameter. Often, environmental health risk analysis is based on a hypothetical, most sensitive individual using a set of health conservative (i.e. high-end exposure) assumptions. Probabilistic distributions for the parameters yield a more informative estimate for risk than a point value for a maximally exposed individual does [34]. Exposure expressions for multimedia pathways need to account for the variability of individual exposure. Such variability includes population movement, individual lifestyles (housing, food and water supply), and the temporal and spatial character of the source. Separate distributions of variable parameters can be used for each subset of the population.

In order to determine the risk to a particular individual, uncertainty and variability must be accounted for separately [7]. We complete a joint uncertainty and variability (JUV) analysis using a nested Monte Carlo simulation to consider uncertainty and variability separately. This method provides a three-dimensional representation with uncertainty and variability on two axes and risk on the third. To perform the nested Monte Carlo analysis, a set of values for the uncertain parameters are randomly selected from their distributions. A Monte Carlo simulation is then performed on the variable parameters by choosing many sets of values for the variable parameters and determining the distribution of risk associated with that set of uncertain parameters.

Another set of values is then selected for the uncertain parameters and we run another Monte Carlo simulation using many sets of variable parameters. This process is then repeated for all the sets of uncertain parameters, hence the name nested Monte Carlo simulation. Resulting values are then sorted along the two axes, uncertainty and variability, with risk plotted on the third axis. From this, the risk for a particular percentile value on each axis can be determined. For example, the distribution representing uncertainty in the risk to the 95th most sensitive person is obtained from the 95th percentile values associated with each set of uncertain parameters. This can be seen more clearly in Figs 1 and 2.

4. Quantitative results

The exposure and risk to individuals living in the mid-western United States were determined as probability distributions. This was accomplished using Monte Carlo simulations to determine the combined effects of parameter uncertainties on the distribution of outcome values. Model inputs are randomly selected using a Latin Hypercube selection process within the Crystal Ball software tool [35]). Each set of parameters is used by the CalTOX spreadsheet to calculate a resulting outcome. The outcomes are then presented as distributions along with the mean value, standard deviation, and 90th percentile value.

Table 7
Mean and standard deviation of the cancer potency factor

Parameter (units)	Distribution shape	Statistical variables
Cancer potency factor (kg day mg ⁻¹)	normal truncated for < 0	0.222 (mean) 0.022 (standard deviation)

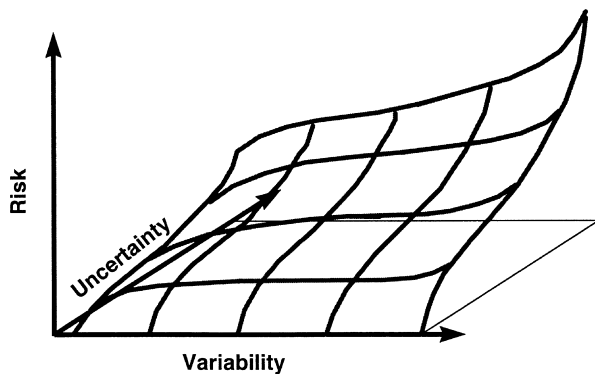


Fig. 1. Risk surface versus the uncertainty and variability axis.

A cumulative probability function resulting from the Monte Carlo simulations for atrazine was prepared for each set of calculations. These functions were used to compare the exposure and risk predicted for childhood and for a lifetime average (including childhood and adult exposure). The exposure and risk to males and females were within 5% of each other and thus we have chosen to display the results of the calculations for just males to demonstrate the types of results and conclusions that can be drawn. There were smaller differences in exposure between males and females than for adults and children. Males were more exposed through inhalation and ingestion of meat than females, while females were more exposed through the ingestion of tap water, fish, and unexposed produce than males.

The cumulative probability functions for males are plotted versus the average daily dose and risk in Figs 3 and 4. The labeled values are for the 90th percentile. The exposure dose and risk for each group differ by a factor of

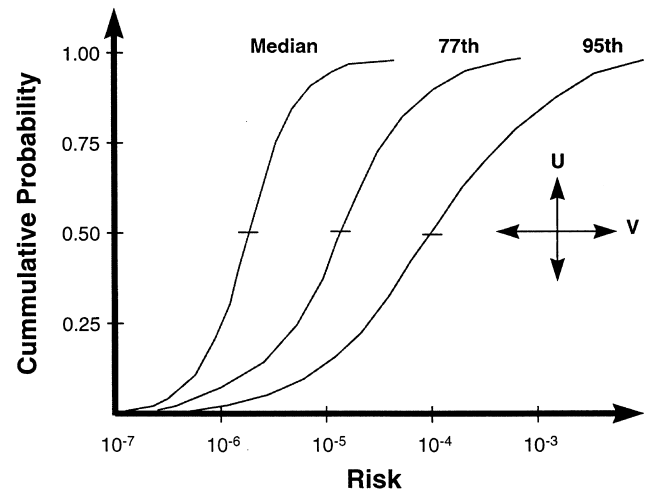


Fig. 2. Cumulative probability with respect to uncertainty for the median, 77th, and 95th percentile values with respect to variability.

two at this percentile and is on the same order of magnitude as other uncertainties in the analysis. The relative difference in exposure between lifetime average parameters and children is greater than the relative difference in risk because the uncertainty introduced by the cancer potency factor is not included in the exposure calculation. Introducing this large uncertainty reduces the difference between the two curves relative to the overall spread of the distributions.

Results based on the exposure and risk averaged over a lifetime are presented in Table 8 while those for childhood exposure are presented in Table 9. A distribution is presented for each exposure pathway. From this information, it is apparent that multiple pathways need to be considered when evaluating the dose from this exposure scenario. The

Table 8
Average lifetime dose for males by exposure pathway and environmental media

Male lifetime calculation	Mean (mg kg ⁻¹ day ⁻¹)	Standard Deviation (mg kg ⁻¹ day ⁻¹)	90th Percentile (mg kg ⁻¹ day ⁻¹)
Inhalation dose	1.5×10^{-07}	3.6×10^{-07}	2.6×10^{-07}
Ingestion doses			
Tap water	6.8×10^{-05}	8.2×10^{-05}	1.4×10^{-04}
Exposed produce	1.8×10^{-04}	1.67×10^{-04}	3.7×10^{-04}
Unexposed produce	1.9×10^{-04}	2.3×10^{-04}	4.3×10^{-04}
Meat	1.4×10^{-07}	1.7×10^{-07}	2.9×10^{-07}
Milk	7.9×10^{-08}	1.1×10^{-07}	1.8×10^{-07}
Eggs	1.5×10^{-10}	2.2×10^{-10}	3.3×10^{-10}
Fish	7.9×10^{-05}	1.1×10^{-04}	1.9×10^{-04}
Soil	2.0×10^{-06}	4.4×10^{-06}	4.4×10^{-06}
Total	5.2×10^{-04}	4.0×10^{-04}	1.0×10^{-03}
Dermal dose	1.4×10^{-04}	3.7×10^{-04}	2.7×10^{-04}
Total dose	6.6×10^{-04}	5.8×10^{-04}	1.3×10^{-03}
Dose from air	8.6×10^{-05}	8.0×10^{-05}	1.8×10^{-04}
Dose from surface soil	1.7×10^{-04}	3.8×10^{-04}	3.5×10^{-04}
Dose from root zone soil	2.0×10^{-04}	2.3×10^{-04}	4.5×10^{-04}
Dose from ground water	5.5×10^{-05}	9.7×10^{-05}	1.3×10^{-04}
Dose from surface water	1.4×10^{-04}	1.5×10^{-04}	2.9×10^{-04}
Lifetime cancer risk	Increased risk 2.3×10^{-05}	Increased risk 3.5×10^{-05}	Increased risk 5.4×10^{-05}

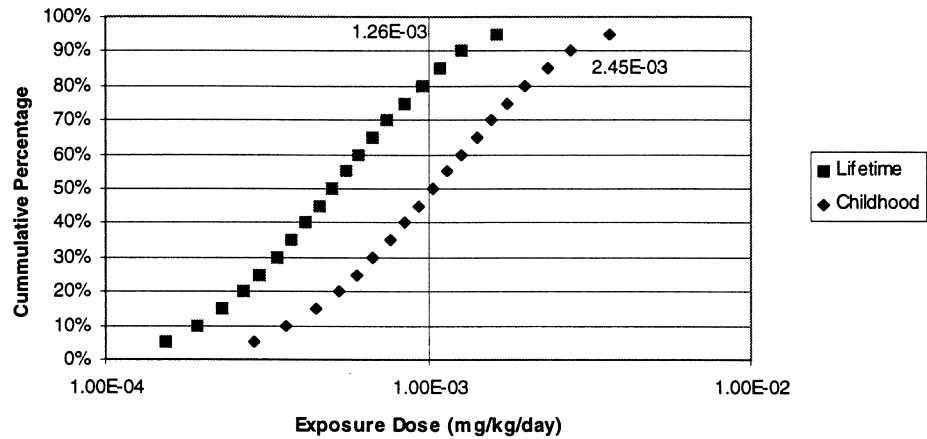


Fig. 3. Cumulative percentage of the distribution of exposure for both childhood and lifetime exposure calculations to atrazine for males.

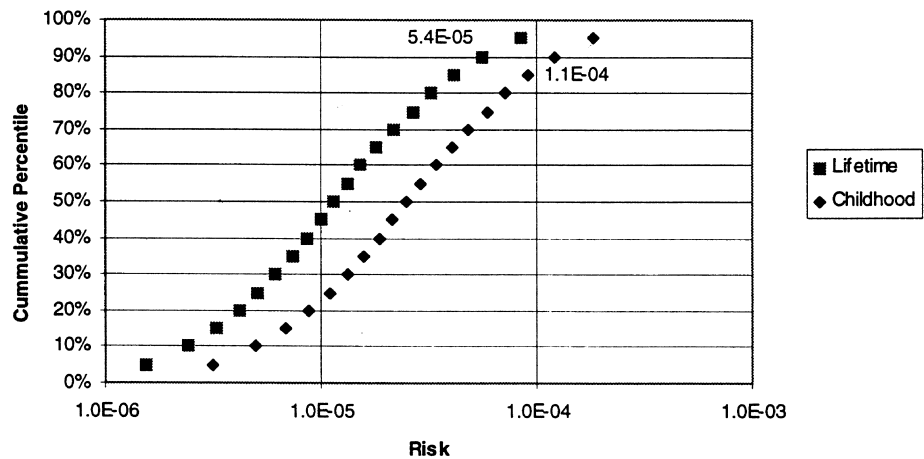


Fig. 4. Cumulative percentage of the distribution of risk for both childhood and lifetime exposure calculations of atrazine for males.

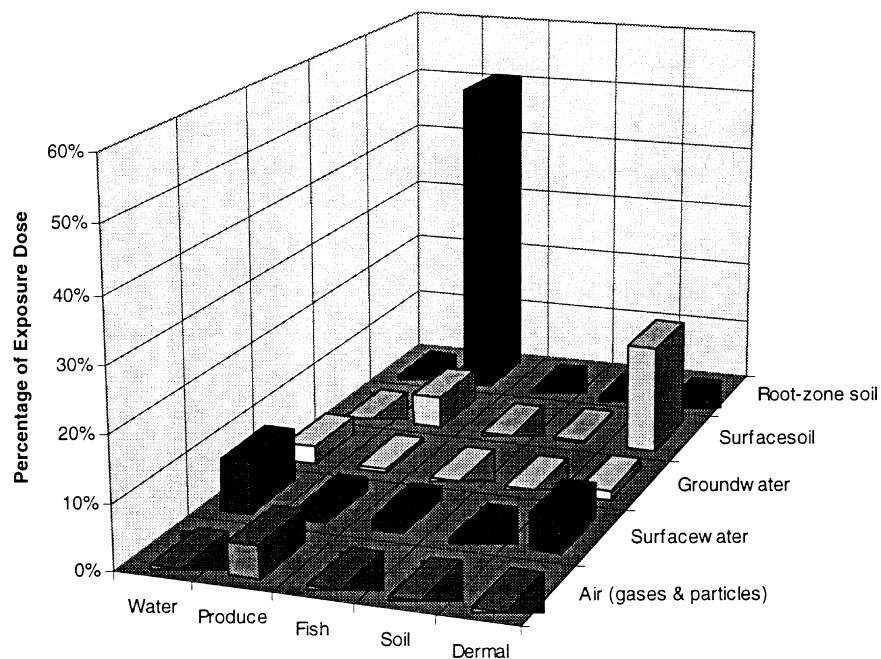


Fig. 5. Percentage of exposure from significant exposure pathways and environmental media, based on point value lifetime exposure parameters.

Table 9
Childhood dose for males by exposure pathway and environmental media

Averaged 0–14 years calculation	Mean (mg kg ⁻¹ day ⁻¹)	Standard deviation (mg kg ⁻¹ day ⁻¹)	90th percentile (mg kg ⁻¹ day ⁻¹)
Inhalation dose	2.9×10^{-07}	2.3×10^{-07}	5.7×10^{-07}
Ingestion doses			
Tap water	1.1×10^{-04}	1.5×10^{-04}	2.2×10^{-04}
Exposed produce	4.3×10^{-04}	4.4×10^{-04}	9.2×10^{-04}
Unexposed produce	3.8×10^{-04}	5.3×10^{-04}	9.0×10^{-04}
Meat	2.2×10^{-07}	3.0×10^{-07}	4.9×10^{-07}
Milk	3.0×10^{-07}	4.0×10^{-07}	6.8×10^{-07}
Eggs	2.1×10^{-10}	5.6×10^{-10}	4.6×10^{-10}
Fish	1.2×10^{-04}	4.4×10^{-04}	2.4×10^{-04}
Soil	7.3×10^{-06}	1.9×10^{-05}	1.7×10^{-05}
Total	1.0×10^{-03}	9.6×10^{-04}	2.2×10^{-03}
Dermal dose	1.9×10^{-04}	4.2×10^{-04}	3.8×10^{-04}
Total dose	1.2×10^{-03}	1.1×10^{-03}	2.4×10^{-03}
Dose from air	2.1×10^{-04}	2.1×10^{-04}	4.4×10^{-04}
Dose from surface soil	3.0×10^{-04}	5.0×10^{-04}	6.8×10^{-04}
Dose from root zone soil	4.2×10^{-04}	5.3×10^{-04}	9.5×10^{-04}
Dose from ground water	8.9×10^{-05}	1.8×10^{-04}	2.1×10^{-04}
Dose from surface water	2.2×10^{-04}	4.7×10^{-04}	4.0×10^{-04}
Lifetime cancer risk	Increased risk 4.6×10^{-05}	Increased risk 7.1×10^{-05}	Increased risk 1.1×10^{-04}

dose from vegetation (i.e. exposed and unexposed produce), dermal exposure, fish, and tap water are all important pathways. It is interesting to note the large standard deviation of the dermal dose.

Tables 8 and 9 also list what portion of the dose results from each environmental medium. The largest doses result from surface soil, root zone soil, and surface water, respectively. The soil compartments are critical because vegetation, a major exposure pathway, is contaminated primarily through the soil. The plant compartment in the multimedia

environment is involved with fate and transport in the environment while the exposure produce concentrations are determined from soil concentrations.

Fig. 5 presents a graphical representation of significant contributions to exposure from various environmental media and exposure pathways based on the point values of each distribution for lifetime averaged exposure parameters. Fifty percent of the exposure comes from produce, 11% comes from water intake and 23% through the dermal pathway. These numbers support the need for multiple pathway exposure assessment for atrazine. In terms of various environmental media; surface water contributes 17% of the exposure, root zone soil contributes 51% and surface soil contributes 22%. The large percentage of exposure resulting from surface water indicates the importance of a multimedia transport model to quantify both fate and risk for atrazine.

The dose and risk to children was calculated and can be compared to a lifetime average exposure and risk. The calculated dose and risk values are presented in Table 9. The difference in exposure between adults and children for each exposure pathway was quantified. The ratio between the exposure to children and exposure over a lifetime was determined at the mean value of each distribution. This ratio varied from pathway to pathway as shown in Table 10, and was greatest for soil, milk, and produce. Although this ratio is greatest for milk and soil, the higher doses to children resulting from these pathways do not have much effect on the overall difference in dose, because these pathways contribute only a small percentage to the overall dose. The increased exposure from the vegetable pathways contributed significantly to the overall difference in exposure between the two groups.

Table 10
Ratio of dose between childhood and lifetime calculations by exposure pathway and environmental medium for the mean and 90th percentile of exposure

Childhood/lifetime	Mean	90th percentile
Inhalation dose	1.92	2.17
Ingestion doses		
Tap water	1.55	1.53
Exposed produce	2.40	2.49
Unexposed produce	1.99	2.12
Meat	1.58	1.69
Milk	3.71	3.77
Eggs	1.42	1.41
Fish	1.47	1.29
Soil	3.73	3.75
Total	2.00	2.10
Dermal dose	1.36	1.42
Total dose	1.87	1.94
Dose from air	2.40	2.43
Dose from surface soil	1.79	1.93
Dose from root zone soil	2.04	2.13
Dose from ground water	1.60	1.61
Dose from surface water	1.50	1.39
Lifetime cancer risk	1.96	1.99

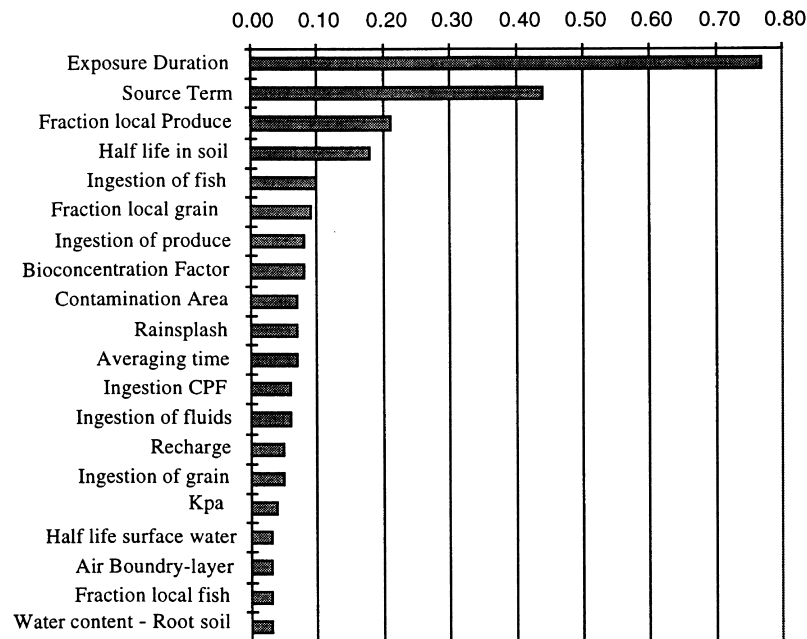


Fig. 6. This chart illustrates the correlation between the variance in the output risk from exposure to atrazine and the variance in 20 input parameters for the calculation of the average lifetime exposure for males.

4.1. Sensitivity analysis

A sensitivity analysis was used to evaluate which parameters have a significant effect on uncertainty. The sensitivity analysis was based on the parameter rank correlation between the output and the defining inputs [36]. In a rank correlation, each input is converted to a rank value, and the correlation coefficient is a measure of the strength of the linear relationship between each input parameter and the calculated output. The sensitivity analysis was based on the exposure parameters averaged over a lifetime.

Fig. 6 illustrates the correlation between the variance in the output risk and the variance in 20 input parameters. Based on contribution to uncertainty, the most significant parameters in descending order are exposure duration, source term, fraction of locally consumed produce, and half-life in soil. The results seem reasonable when compared with the predominant exposure pathway, vegetation, because the amount of locally consumed produce affects the exposure through this pathway, as does the reaction half-life in soil, by reducing the atrazine concentration in the soil and thus in the vegetation. The results of this sensitivity analysis indicates that the risk is sensitive to both uncertain and variable parameters, indicating that they are equally well characterized.

4.2. Joint uncertainty and variability analysis

Two joint uncertainty and variability calculations were completed for atrazine. Both calculations were based on a 14-year exposure duration, one using exposure parameters averaged over childhood and the other using parameters

averaged over a lifetime. The variable parameters were defined as the inter-individual variable parameters while all other parameters were defined as the uncertain parameters. While there may be some parameters that could be argued as variable parameters used in the determination of the exposure concentration, they were defined as uncertain parameters for this case. A nested Monte Carlo simulation was then completed using 500 values for the uncertain parameters generated from a Latin Hypercube simulation, and 500 values for the variable parameters, also generated from a Latin Hypercube simulation.

The results can be seen in Fig. 7. The amount of uncertainty in the calculation can be judged by looking at the range of a single percentile of variability. The effect of the variability can be determined by viewing the separation between the line for the 50th percentile and 90th percentile lines. The effect of the difference between lifetime exposure as compared to the childhood average exposure can be interpreted by viewing the difference between the values for any percentile line.

Because the distance between lines of variability and lines of uncertainty are approximately equal, it is apparent that the variance resulting from both uncertain and variable parameters are significant. For this well characterized contamination scenario, accuracy in quantifying exposure can be gained by considering children separately.

5. Summary and conclusions

The herbicide atrazine is selected as the sample contaminant for the health and environmental risk assessment presented

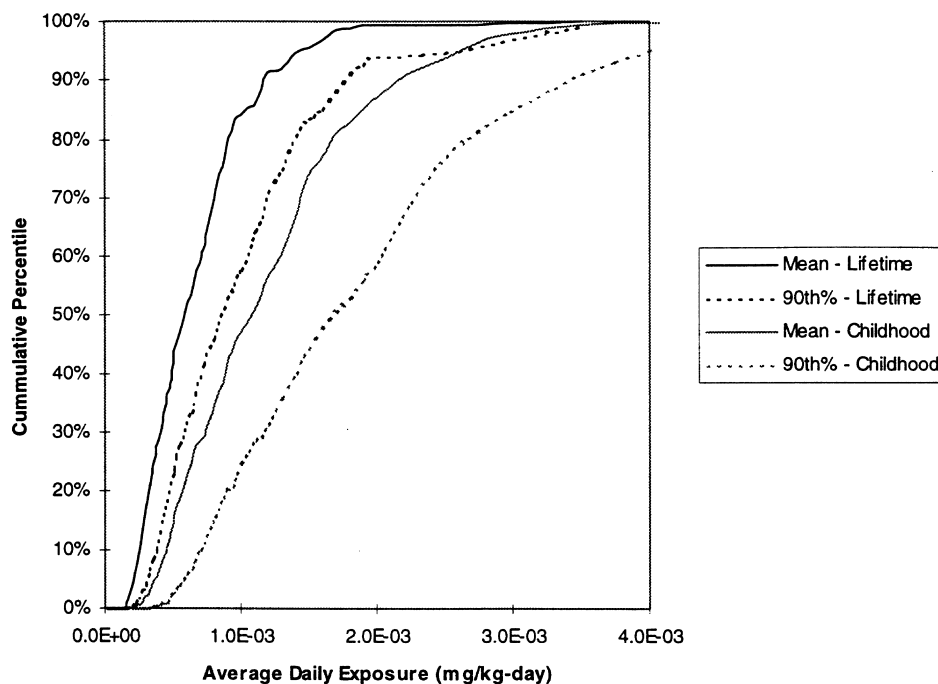


Fig. 7. Joint uncertainty and variability distribution for calculations of exposure made using parameters averaged over childhood and a lifetime.

in this paper because of its widespread use in the US. Monte Carlo simulations are used to illustrate and account for the effects of uncertainty and variability in fate, transport, exposure and risk. Uncertainties associated with the input parameters can involve the physical and chemical properties of the contaminant, landscape characteristics, exposure parameters, and biological dose response. The source of such uncertainties can be attributed to complexities in site characterization, transport and fate modeling, exposure calculations, and extrapolation of toxicological and carcinogenic effects.

Uncertainty and variability are propagated through the model by stochastic methods. The results of the Monte Carlo simulations performed in this paper can be summarized as follows. The mean estimated added lifetime cancer risk is on the order of 10^{-5} with the standard deviation on the same order of magnitude. The 90th percentile lifetime cancer risk is less than 10^{-4} .

There are a number of exposure pathways that have a significant contribution to the overall dose. Ingestion of produce, dermal uptake of surface soil, ingestion and dermal uptake of surface waters are the largest contributors. The exposure to children is 1.6 times greater than the average lifetime exposure at the 90th percentile.

Possible weaknesses with this analysis include the lack of a mid-western site-specific exposure duration. As determined in the sensitivity analysis, this is an important parameter. The exposure duration in a farming community might exceed the national average, and thus would be only represented in the higher percentiles of the national distribution. It should also be noted that a large proportion of the risk comes from surface water and the local percentage of surface water in tap and irrigation water could have a

large influence on the exposure. Again, a distribution was used for the parameter and thus the proper ratio was considered in this range. Finally, occupational exposure was not considered. There would be more atrazine tracked into the home if one member of the household worked with atrazine than was accounted for by the pathway for outside soil being tracked into the home.

The health risk assessment of an agrochemical can determine the hazards associated with human exposure to the substance in question. We have completed an analysis of the exposure and evaluated the uncertainties and variabilities faced during the exposure assessment of atrazine with joint uncertainty and variability analysis using nested Monte Carlo methods. The research completed in preparation of this paper yielded the following conclusions:

1. Results of this study indicate that atrazine exposure comes from a variety of sources and thus a multimedia, multiple pathway exposure model is necessary to provide a complete picture of human exposure. As a result, a simple, multimedia model may be more appropriate than a complex model focusing primarily on a single exposure pathway, possibly ignoring a large part of the exposure.
2. The application of Monte Carlo methods in the CalTOX model enables the user to propagate uncertain parameter values found in the literature in order to develop a distribution of the outcome risk. Sensitivity analysis indicate that the exposure duration, source term, fraction of local produce, and reaction half-life in soil can affect calculation results more directly than other model parameters.

3. The joint uncertainty and variability analysis indicates both true uncertainty and inter-individual variability have a significant effect on overall variance. This confirms the results of the sensitivity analysis which indicates both types of parameters are important, and confirms the need to examine uncertainty and variability in a disaggregated fashion.
4. The predicted exposure based on parameters averaged over a child's life is 1.6 times greater than the corresponding lifetime calculation. While this is not an overwhelming difference when compared to other sources of uncertainty, it is significant, indicating that, for this exposure scenario, it is important to consider children as a separate subgroup of the population.
5. Since large amounts of atrazine have been used in the United States, the resulting public health risk cannot be ignored, even though evidence has not conclusively linked atrazine exposure to adverse health effects such as cancer. When atrazine is present in agricultural fields, ground, or surface water, humans can be exposed via contact with, or ingestion of, contaminated water, soil, livestock, or food crops. The potential for exposure resulting from higher concentrations in air, water, and soil are especially prevalent during spring, the period of heaviest use.

The quality of available parametric data and the nature of the uncertainties associated with each parameter must be examined carefully so risk managers can properly judge the significance of the calculated risk. Improvement of parametric values can yield more confidence in risk estimates, and hence, decisions made based on these estimates. Disaggregating uncertainty and variability for both children and adults allows decision makers to evaluate sources of uncertainty versus inter-individual variability, and to evaluate children as a separate subgroup. It is recommended that any proposed reforms to US pesticide laws should reflect current scientific knowledge regarding techniques of risk analysis when determining the tradeoffs between agrochemical impacts on public health and the advantages of agrochemicals.

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